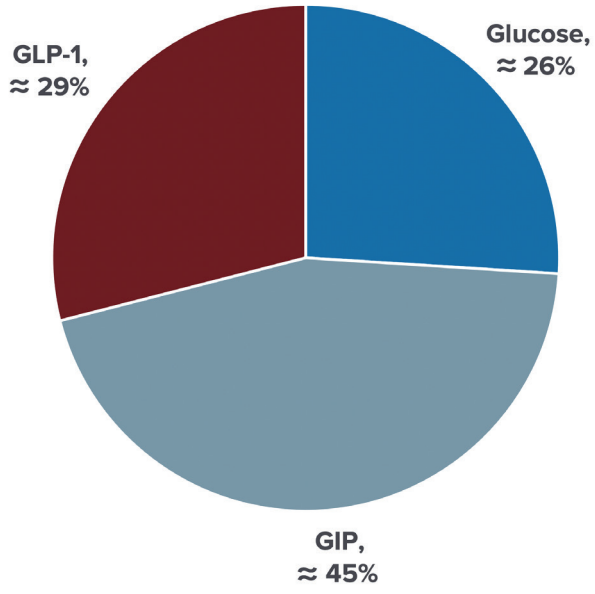
Medscape EDUCATION

The New Side of Incretin-Based Therapy in Type 2 Diabetes: Exploring Advances From EASD 2021

The Incretin Effect

The incretin effect describes the body's natural release of insulin in response to high postprandial glucose levels. Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are hormones that stimulate insulin secretion from beta cells in a glucose-dependent manner (ie, insulinotropic actions). The insulinotropic actions of GIP and GLP-1 are additive and responsible for about 75% of postprandial insulin secretion (Figure 1).

Figure 1. GIP and GLP-1 Are Responsible for About 75% of Postprandial Insulin Secretion.

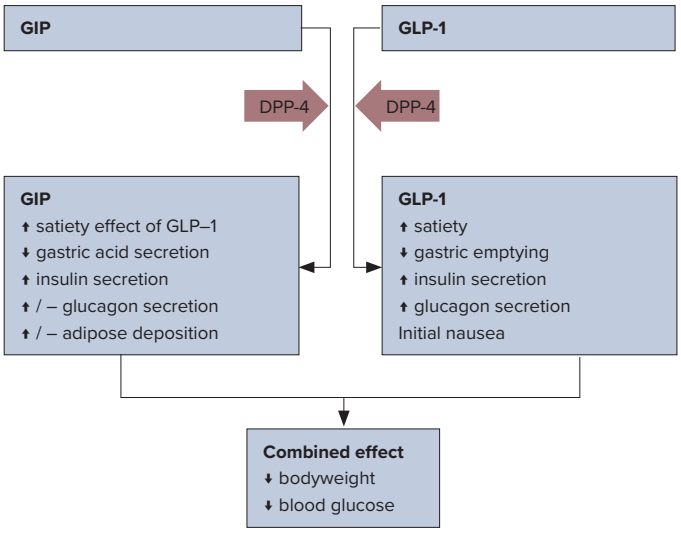


There is also evidence that GIP and GLP-1 have complementary extra-glycemic effects beyond glucose control. Growing evidence suggests there is a need to treat obesity, not just glycated hemoglobin (HbA1c), in patients with type 2 diabetes (T2D) to help in the prevention and management of cardiovascular disease, nonalcoholic steatohepatitis, and other weight-related comorbidities.

The Rationale for Combining T2D Treatment Targets

Together, GLP-1 and GIP may have a synergistic effect, resulting in a greater effect on glucose levels and body weight in people who have T2D. (Figure 2)

Figure 2. GIP and GLP-1 Effects



- GLP-1 improves glucose-dependent insulin secretion from beta cells, reduces glucagon secretion, and decreases the rate of gastric emptying. This hormone also reduces appetite and increases satiety via the hypothalamus, contributing to weight loss.
- GIP improves glucose-dependent insulin secretion from beta cells. In adipose tissue, GIP plays a role in carbohydrate and lipid metabolism via regulating glucose uptake and lipolysis. This hormone also activates some neurons in the brain that are distinct from GLP-1 that reduce appetite, and thus its effects on weight may also be additive to GLP-1.

New Data From the European Association for the Study of Diabetes (EASD) 2021: An Emerging Dual Mechanism Incretin-Based Agent

SURPASS-3: Once-Weekly Tirzepatide vs Once-Daily Degludec (Phase 3, 52 Weeks)

In patients with T2D inadequately controlled on metformin, tirzepatide – a dual GIP/GLP-1 receptor agonist – at a dose of 5 mg, 10 mg, and 15 mg reduced HbA1c from baseline by 1.93%, 2.20%, and 2.37%, respectively, vs 1.34% for insulin degludec ($P < .0001$). All 3 tirzepatide doses decreased body weight (–7.5 kg to –12.9 kg), whereas insulin degludec increased body weight by 2.3 kg. Gastrointestinal side effects were the most common reported adverse event with tirzepatide.

SURPASS-3 MRI Substudy

In a subset of patients from SURPASS-3 (N = 296), tirzepatide 10 mg and 15 mg once weekly led to a significantly greater reduction from baseline in liver fat content compared to titrated insulin degludec at 52 weeks. Liver fat content has been shown to contribute to complications of diabetes, particularly cardiovascular (CV) complications.

SURPASS-4: Once-Weekly Tirzepatide vs Insulin Glargine (Phase 3, 52+ Weeks)

All 3 doses of tirzepatide significantly reduced HbA1c and body weight from baseline compared with titrated insulin glargine (all $P < .0001$) in patients with high CV risk and uncontrolled T2D despite treatment with oral glucose-lowering medications. Tirzepatide was not associated with excess CV risk compared with insulin glargine. Common adverse events with tirzepatide were nausea, diarrhea, and vomiting, most of which were mild to moderate and were transient.

Other "GLP-1-Enhancing" Treatment Strategies Under Clinical Investigation

In addition to dual GIP/GLP-1 receptor agonism, several other multi-agonists are being investigated for the treatment of T2D and obesity under the concept that GLP-1 restrains the hyperglycemic action of glucagon while allowing it to exert its beneficial actions on body weight and lipid metabolism. These multi-agonists include:

- GLP-1/GIP/glucagon receptor tri-agonist (LY3437943). Phase 1 trial complete, phase 2 trials ongoing
- GLP-1 receptor agonist plus a long-acting amylin analogue (cagrilintide). Phase 1 and phase 2 trial data reported
- Once-weekly basal insulin (icodec) in combination with once-weekly semaglutide
- Once-daily oral GLP-1 RA (LY3502970). Phase 1 trial completed

High Dose GLP-1 Receptor Agonists

The once-weekly GLP-1 receptor agonists, dulaglutide and semaglutide, have demonstrated greater glycemic and weight loss benefits in patients with inadequately controlled T2D when given at higher doses -- dulaglutide 3 mg to 4.5 mg and semaglutide 2 mg -- compared with standard doses, while maintaining a similar safety profile. A phase 3 trial evaluating high-dose oral semaglutide 25 mg to 50 mg daily vs standard dose in patients with T2D has been initiated.